Part #6

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: A. Tadepalli, et al. ART UNIT: 125

SERIAL NO.: 07/715,439

DOCKET NO.: 38942-DIV EXAMINER: Jordan

FILED: June 14, 1991

FOR: Compounds for Use in Medicine

Honorable Commissioner of Patents and Trademarks

Washington, DC 20231

Sir:

DECLARATION OF Walker Anderson Long

UNDER RULE 1.132

I, Walker Anderson Long, do hereby declare that:

1. I am an employee of Burroughs Wellcome Co., an assignee of the above identified U.S. Application Serial No. 07/715,439.

2. Attached hereto as EXHIBIT A are relevant structures.

3. Attached hereto as EXHIBIT B is a listing of cited references 1 through 7.

4. Attached hereto as EXHIBIT C is a document disclosing my background.

5. The cited Aristoff et al.[1] teaches that certain benzindine prostaglandins are capable of lowering blood pressure in rats. The assay which was used to determine this effect measures changes in systemic blood pressure, not pulmonary blood pressure. Assays which measure changes in pulmonary blood pressure are always identified by those skilled in the art as measuring "pulmonary arterial" or "capillary wedge" pressures. Therefore, the assay which was used by Aristoff et al. would not teach the effect of these

compounds on pulmonary blood pressure. Furthermore, there is no correlation between the effects of benzindine prostaglandin compounds on the systemic and pulmonary circulations. In fact, the effects of a given agent on the two circulations are often contradictory. This paradox is especially characteristic of prostaglandin-type compounds. For example, in adult animals the prostaglandin derivatives PGD_2 and PGE_2(figures 1 and 2) vasodilate the systemic circulation(reduce blood pressure) but vasoconstrict the pulmonary circulation and actually cause pulmonary hypertension[2,3,4,5]. Therefore, by knowing the effect of a particular benzindine prostaglandin on the systemic circulation, one could not predict its effect on the pulmonary circulation.

Very minor structural differences between prostaglandin derivatives can cause diametrically opposite effects in the systemic and pulmonary circulations, resulting in the complete reversal of a given effect in a given circulation. The only structural difference between PGE_1(figure 3) and PGE_2(figure 2) is that PGE_1 lacks the side-chain double bond present in PGE_2. Both PGE_1 and PGE_2 are systemic vasodilators. However, PGE_1 is a pulmonary vasodilator whereas PGE_2 exhibits the

opposite effect on the pulmonary circulation and is a pulmonary vasoconstrictor[2,5]. Clearly, each prostaglandin compound or analog has unpredictable effects on the pulmonary and systemic circulations. From the information disclosed in the cited Aristoff et al. paper(i.e., that these compounds lower systemic blood pressure) one could not predict the effect they would have on the pulmonary circulation. Therefore, the Aristoff et al. paper does not teach that the compounds of the present invention would have utility in the treatment of pulmonary hypertension.

The cited Rubin et al.[6] paper teaches that prostacyclin(PGI_2, figure 4), which is a non-benzindene prostaglandin, reduces pulmonary hypertension. However, as shown in figures 4 and 5, the structural differences between the benzindine prostaglandins of the present invention(figure 5) and the non-benzindene prostaglandin derivative prostacyclin(figure 4,) are quite significant and one cannot consider the two compounds to be equivalent. As stated above, even very minor structural differences between prostaglandin derivatives can lead to completely opposite effects on the pulmonary circulation(or on the systemic circulation). A case in point compares PGE_2 with

prostacyclin(PGI_2); the structure of PGE_2(figure 2) is identical to prostacyclin(figure 4) except that it does not possess a double ring structure. Although prostacyclin and PGE_2 are both systemic vasodilators, they have opposite effects on the pulmonary circulation. In adult animals or adult humans, prostacyclin is a pulmonary vasodilator whereas PGE_2 is a pulmonary vasoconstrictor[2,5,7]. The minor structural difference causes the two compounds to have opposite effects on the pulmonary circulation. Thus, by knowing the effect of prostacyclin on the pulmonary system, one could not predict the pulmonary effect of related compounds. Since the structures of the benzindene prostaglandin compounds of the present invention are significantly different from prostacyclin(figures 4 and 5), the effect of these compounds on pulmonary pressure could not be predicted by knowing the effect of prostacyclin on pulmonary pressure. Therefore, the Rubin et al. paper does not teach that the compounds of the present invention would have utility in the treatment of pulmonary hypertension.

In conclusion, the Aristoff et al. paper teaches that several prostaglandin compounds can cause lowering of systemic blood pressure. However, by knowing the

effect that a particular prostaglandin compound has on the systemic circulation, one cannot predict the effect that it will have on the pulmonary circulation. In addition, even minor structural differences between prostaglandin-type compounds can lead to completely opposite effects on the pulmonary circulation. Therefore, knowledge of the pulmonary effect of a prostaglandin-type compound is not predictive of the pulmonary effect of another prostaglandin-type compound.

The undersigned declares that all statements made herein of declarant's knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Declarant: Walter A. Long

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